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A. D. MELVIN, CHIEF OF BUREAU.

THE ORIGIN OF THE RECENT OUTBREAK
OF FOOT-AND-MOUTH DISEASE
IN THE UNITED STATES.

BY

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LETTER OF TRANSMITTAL.

U. S. DEPARTMENT OF AGRICULTURE,
BUREAU OF ANIMAL INDUSTRY,
Washington, D. C., April 24, 1909.

SIR: I have the honor to transmit herewith and to recommend for publication as a circular of this Bureau a report by Dr. John R. Mohler, chief of the Pathological Division of this Bureau, and Dr. Milton J. Rosenau, director of the Hygienic Laboratory of the United States Public Health and Marine-Hospital Service, of an investigation into the origin of the recent outbreak of foot-and-mouth disease in the United States.

On November 10, 1908, this disease was discovered among cattle in Pennsylvania, and a few days later it was found also in Michigan, New York, and Maryland. In view of the strict quarantine maintained by the Bureau on imported live stock and the fact that the importation of ruminants from countries where foot-and-mouth disease existed was prohibited entirely, it seemed highly improbable that the infection was brought in with animals, and various other ways in which it might have gained entrance into the United States were suggested, as that immigrants carried the virus on their clothing, that it was brought in on hay or straw used for packing, or that it was introduced in biological products. When, therefore, the disease was traced by the Bureau's inspectors to calves that had been used in propagating smallpox vaccine by a Detroit establishment, and the cases of longest standing were found among these calves, it was considered probable that the vaccine was contaminated with the virus of foot-and-mouth disease and that this caused the outbreak, especially since vaccine had been suspected of being responsible for the New England outbreaks of 1902-3.

When suspicion was thus directed to the vaccine virus of the Detroit establishment it was decided to make an investigation to determine this point; and as the United States Public Health and Marine-Hospital Service of the Treasury Department is charged by law with the supervision of biological products used in human medicine, that Service was requested to join this Bureau in making the proposed investigation. The work was confided to Doctors Mohler and Rosenau, and the results are given in the report herewith presented.

It is evident from their tests, which were carried out in accordance with careful scientific methods, that the recent outbreak of foot-and-mouth disease was caused by the propagation of vaccine virus which had been contaminated with the virus of foot-and-mouth disease, and that the contaminated strain of vaccine originally came from some foreign country where the disease prevailed. In some of their tests Doctors Mohler and Rosenau used animals which had been vaccinated and were therefore immune to vaccinia or cowpox, so that, in case the infection of foot-and-mouth disease was present in the vaccine under suspicion, the lesions of that disease would not be suppressed or obscured by those of vaccinia. By this method and by means of intravenous inoculation they were able to detect the contaminating infection when it might not otherwise have been disclosed. In the light of the evidence obtained as to the origin of the recent outbreak it now seems probable that the New England outbreaks of 1902-3 were due to the same cause.

Although the foot-and-mouth disease has been eradicated after vigorous work by this Department and Bureau in cooperation with the State authorities, the facts disclosed by this report show that the country is in constant danger of having this and other contagious diseases of live stock introduced from abroad in spite of all the precautions that the Department is able to take under existing legislation. The United States Public Health and Marine-Hospital Service already has power, under the act of Congress of June 1, 1902, to control the importation of biological products used in the prevention or treatment of diseases of man, and I consider it highly important that similar control should be given by law to the Secretary of Agriculture over similar products when intended for the treatment of domestic animals.

Respectfully,

A. D. MELVIN,
Chief of Bureau.

HON. JAMES WILSON,
Secretary of Agriculture.

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THE ORIGIN OF THE RECENT OUTBREAK OF FOOT-AND-MOUTH DISEASE IN THE UNITED STATES.

NATURE AND CHARACTERISTICS OF THE DISEASE.

Foot-and-mouth disease, also known as apthous fever, epizootic apthia, and *eczema contagiosa*, is an acute, highly communicable disease chiefly confined to cloven-footed animals and characterized by an eruption of vesicles on the mucous membrane of the mouth and on the skin between the toes and above the hoofs. The vesicles rupture, forming erosions and ulcerations; there is also salivation, tenderness of the affected parts, loss of appetite, lameness, emaciation, and diminution in the quantity of milk secreted.

The tremendous ravages of the disease are seen in the number and variety of the species attacked. While it may be regarded as essentially a disease of cattle, hogs would seem to be as easy a prey. Almost in the same grade of receptivity are sheep and goats. Next in order of susceptibility come the buffalo, American bison, camel, chamois, llama, giraffe, and antelope. Horses, dogs, cats, and even poultry, may occasionally become infected with the disease, the last three being particularly dangerous as carriers of the contagion. Man himself is not immune, and the frequency of his infection by coming in contact with diseased animals is established by numerous observations.

The disease prevails in European countries and occasions great economic losses. The mortality is quite low, the serious losses depending chiefly upon the diminution of the milk secretion and the loss of flesh in the affected animals.

Foot-and-mouth disease has made its appearance in the United States only on five different occasions—1870, 1880, 1884, 1902–3, and 1908. Its spread is very rapid among cattle, owing to the highly communicable character of the contagion, but fortunately every outbreak upon American soil has thus far been quickly followed by its complete suppression.

The causative agent of this disease has not been isolated, although numerous attempts have been made to cultivate and stain it. The experiments of Loeffler and Froesch in 1898 have shown that the virus will pass through the finest porcelain filters, thus indicating its

ultramicroscopic size and the reason it has not been detected by staining methods.

The specific principle may be found in the serum of the vesicles in the mouth and on the feet and udder; in the saliva, milk, and various secretions and excretions; also in the blood during the rise of the temperature. Animals may be infected directly, as by licking, and in calves by sucking, or indirectly by fomites such as infected manure, hay, utensils, drinking troughs, railway cars, animal markets, barnyards, and pastures.

No definite immunity is rendered by an attack. The period of incubation is variable, usually from two to six days. The disease may appear in twenty-four hours after exposure. In exceptional instances the period of incubation is prolonged to fifteen or even eighteen days.

FOOT-AND-MOUTH DISEASE IN MAN.

Foot-and-mouth disease is primarily and principally a disease of cattle; secondarily and casually, a disease of man. The disease is transmissible to man through the ingestion of raw milk, buttermilk, butter, cheese, and whey from animals suffering from foot-and-mouth disease. It is also transmitted directly, though more rarely, from the salivary secretions or other infected material which may gain entrance through the mucous membrane of the mouth. It is doubtful whether the disease can be transmitted to man by cutaneous or subcutaneous inoculation, though it is probable that the infection may be communicated if the virus directly enters the blood through wounds of any kind. Children are not infrequently infected by drinking unboiled milk during the periods in which the disease is prevalent in the neighborhood, while persons in charge of diseased animals may become infected through contact with the diseased parts or by milking, slaughtering, or caring for the animals.

The symptoms in man resemble those observed in animals. There is fever, sometimes vomiting, painful swallowing, heat and dryness of the mouth, followed by an eruption of vesicles on the buccal mucous membrane and very rarely by similar ones on the fingers. The vesicles appear on the lips, gums, cheek, and edge of the tongue, and are about the size of a pea. The vesicles soon rupture, leaving a small erosion which is soon covered by a thin crust under which the new formation of epithelium proceeds rapidly. The skin eruption mostly appears on the hands, tips of the fingers, base of the nails, volar surfaces of the finger tips, and more seldom on the toes and other parts of the body. Besides these local changes, during the course of the disease there are occasionally observed headache, pain in the limbs, vertigo, abdominal cramps, vomiting, diarrhea, and weakness. The disease is very seldom fatal, usually appearing in a very mild form

except in weakened children, in whom an accompanying intestinal catarrh may lead to a fatal termination.

Veterinarians who have had considerable experience with the disease among animals regard the human affection as by no means uncommon in countries where foot-and-mouth disease prevails, but the disturbance of health is usually too slight to come to the notice of the family physician.

Valentin was probably the first to suggest the infectiousness of milk and the transmissibility of the virus to man through the milk of diseased animals. He reported several cases where people became infected during the outbreak in Hesse in 1695. Sagar in 1765 reported a similar infection of men in Moravia from drinking infected milk. In 1778 all the residents of an Austrian monastery developed a vesicular eruption in the mouth after drinking infected milk.

Hertwig, Mann, and Villain conducted an experiment on themselves in 1834 by drinking milk warm from a cow suffering with an attack of foot-and-mouth disease. Five days later vesicles appeared on the hands, fingers, tongue, cheeks, and lips of Hertwig, while the eruption in the other two was confined to the buccal mucous membrane.

Allbutt observed the vesicular eruption in the mouths of three children in Yorkshire during the English outbreak in 1883, and obtained information of a number of similar cases in the community.

During the 1883 outbreak in Germany a shepherd apparently infected himself by holding in his mouth a knife which had just been used in paring the diseased feet of his sheep. During this outbreak a number of milkmaids were infected through milking, the vesicles appearing principally on their hands.

In the Berlin outbreak of 1895 a number of those who drank infected milk developed fever, followed by the formation of vesicles on the tongue and lips. The acute disease lasted about five days, leaving a feeling of weakness for some time. Virchow made an investigation of these cases and unhesitatingly pronounced the affection to be foot-and-mouth disease.

A collection of the cases of this disease transmitted to man through the consumption of milk has been prepared by Wurzburg, while the work of Bussenius and Siegel contains a full bibliography of the literature of such transmissions up to 1896.

Instances resulting from the use of butter made from infected milk are on record, while Schneider mentions instances where human infection followed the consumption of infected cheese. Friedberger and Fröhner record cases which were caused by infected buttermilk.

But few outbreaks of the disease have occurred in the United States, and therefore cases of its transmission to man in this country

are quite rare. Law reports having observed the disease in man from drinking infected milk during the epizootic of 1870 in the Eastern States, but the outbreaks of 1880 and 1884 affected such a small number of animals and were so quickly suppressed that no instance of its transmission to man was recorded. A few cases have been reported by Brush^a accompanying the New England outbreak of 1902. Similar reports have been likewise received concerning the appearance of vesicular eruptions in the mouths of children during the 1908 outbreak, and the history of these cases incriminates the milk supply.

Experiments by Loeffler and Froesch,^b as well as recent experiments which have been made in Denmark and Germany, indicate that the infection is comparatively easy to destroy by heat or the usual antiseptics. Milk pasteurized at a temperature of 60° C. for twenty minutes is safe so far as infection by foot-and-mouth disease is concerned.

HISTORY OF RECENT OUTBREAKS.

On October 26, 1908, two carloads of cattle infected with or exposed to foot-and-mouth disease were sent from the stock yards at East Buffalo, N. Y., to Watsonstown and Danville, Pa., respectively, from which points the disease was distributed to nine separate farms. It was upon these farms that the disease was brought to the attention of Dr. Leonard Pearson, State veterinarian of Pennsylvania, who in turn notified the United States Department of Agriculture on November 10, and the diagnosis was confirmed on November 11 by Dr. A. D. Melvin, Chief of the Bureau of Animal Industry, and Drs. Rice P. Steddom and John R. Mohler, chiefs, respectively, of the Inspection and Pathological divisions of the Bureau.

An endeavor was at once made to trace the disease from the affected cattle back to the point of origin, but at that time it was impossible to obtain any definite clew regarding the source of the infection which would lead beyond the Buffalo stock yards. The only information which seemed at all significant was the fact that five bulls in the carload lot which went to Watsonstown and two bulls in the car which went to Danville originated in the shipment of Mr. J. Jackson, living in the central portion of the State of Michigan. In order that this clew should be run down as quickly as possible, an inspector was at once detailed to look up the origin of this shipment, while other inspectors at the same time were sent to points in Canada, Ohio, New York, and Indiana for the purpose of investigating the condition of the cattle remaining at the farms where originated the

^a Journal of the American Medical Association, vol. 40, June 20, 1902, p. 1700.

^b Centralblatt für Bakteriologie, Parasitenkunde und Infektionskrankheiten, 1. abt., vol. 23, 1898, p. 371.

[Cfr. 147]

balance of the cattle in the two carload lots which went to Watson-town and Danville from Buffalo. Reports from all these inspectors were duly received and proved to be entirely negative.

Subsequently (on November 22) a suggestive telegram was received from the Bureau of Animal Industry's inspector in charge at Detroit, Mich., and another telegram was received from a local veterinarian in the same city stating that a mild type of foot-and-mouth disease was prevailing on several farms in that vicinity. This diagnosis was confirmed on the following day, and it developed that among the animals infected with foot-and-mouth disease were 21 heifers which had previously been used by Manufacturer A for the production of vaccine virus. This fact caused Secretary of Agriculture James Wilson and Doctor Melvin, both of whom had gone to Detroit to make a personal investigation of the outbreak, to suspect the contamination of the vaccine material used; and inasmuch as the United States Public Health and Marine-Hospital Service, under the act of Congress of July 1, 1902, is charged with the supervision of biological products used in the prevention and treatment of diseases of man, the Secretary requested the cooperation of that Service in an investigation, which was carried out by the writers of this paper. The character of the lesions in the mouths and on the feet of the above-mentioned animals indicated that they were in the fourth stage of the disease, or the stage of healing, and that these lesions were older and more nearly healed than those found in any other center where the infection had been observed.

For these reasons, together with the fact that the outbreaks of foot-and-mouth disease in 1902 and 1903 were quite closely associated with the vaccinated cattle of the New England Vaccine Company's establishment and Dr. E. E. Tyzzer's experimental work with vaccine at a farm at Wakefield, Mass., it was deemed advisable to make a thorough investigation of the movements of the 21 vaccinated cattle above referred to, and to ascertain if possible what connection, if any, the use of these cattle for the production of vaccine virus by Manufacturer A had with the origin of the 1908 outbreak of foot-and-mouth disease.

The outbreak of foot-and-mouth disease in Massachusetts during 1902 started in Chelsea, and the place where it was thought to have originated was the farm of Mr. Owen Clark, who had a contract with Doctor C., of the New England Vaccine Company, to rent calves for the propagation of vaccine virus. These calves were later returned to Mr. Clark after the vaccine virus had been secured. Doctor C. occasionally obtained seed vaccine from outside sources to either strengthen or improve his product. He admitted having obtained a foreign strain, presumably of Japanese origin, through Manufacturer

B, during the summer of 1902, while the outbreak in Mr. Clark's herd occurred in August of the same year. Although suspicion was directed to this source of origin of the 1902 outbreak, it was finally concluded that, as Mr. Clark's place was so near to Massachusetts Bay and the docks, there was some likelihood of the contagion having reached his farm through infected hay, straw, fodder, or other material from the trans-Atlantic steamers, and this explanation was quite generally accepted in lieu of more definite evidence.

Later an independent outbreak of foot-and-mouth disease was started at Wakefield, Mass., in August, 1903, by Dr. E. E. Tyzzer, of Harvard Medical School, who was doing some experimental work in the study of vaccine bodies. He inoculated some calves on his father's farm with seed vaccine obtained from Doctor K. It was said that this virus also came from Japan, through Manufacturer B. As a result foot-and-mouth disease developed not only in the inoculated calves, but in the milch cows on the farm as well. The State of Massachusetts and the Bureau of Animal Industry subsequently had Doctor Tyzzer repeat the experiments at an isolated stable in Wakefield that was rented for the purpose, and foot-and-mouth disease was again produced in this second series of inoculated cattle by the use of the same sample of vaccine virus.

There is no question that Tyzzer succeeded in producing foot-and-mouth disease as a result of inoculation of vaccine virus which in some way had become contaminated with the virus of foot-and-mouth disease, and in his report to Doctor Salmon, then Chief of the Bureau of Animal Industry, he wrote:

The mouth lesions and the vesicles occurring on the udders of the experiment animals presented a special type of necrosis and represent a process entirely distinct from vaccinia. * * * Two cows having passed through the eruptive disease described in this report were not immune to vaccinia, as has been shown by the inoculation of vaccine lymph and the subsequent microscopical study of the lesions.

Drs. U. G. Houck and G. A. Johnson, who had been designated by the Bureau of Animal Industry to make clinical notes on these cases, state in their report that "the vaccine lymph used on both herds was responsible for the conditions that developed in them; that is, the production of a contagious disease, which, if it is not foot-and-mouth disease, the symptoms and lesions defy a differential diagnosis."

However, there have always been an element of doubt and some contention with reference to the manner in which this vaccine became contaminated. The possibility that this vaccine virus, which had been removed from its original container, was contaminated by placing it in an ice chest with specimens of foot-and-mouth disease at once suggested itself to Doctor Salmon. This, however, does not seem at all certain, particularly in the light of our present knowledge,

although this view was apparently strengthened by the fact that four different series of experiments conducted at that time with vaccine obtained from the original source failed to produce any lesions recognized by the investigators as due to foot-and-mouth disease. The coincidence of having this outbreak occur in the quarantined section only two or three months after the last cases of the previous outbreak had been eradicated threw further doubt upon the contamination of the vaccine virus.

With these facts in mind, and with the knowledge that the 21 vaccinated cattle of Manufacturer A were among the first to show foot-and-mouth disease in the present outbreak, the writers proceeded to the laboratories of this manufacturer, arriving November 30, 1908. The movements of these cattle were at once investigated, with the result shown in figure 1.

These cattle were purchased in September by Shaw Brothers, who had a contract with Manufacturer A to furnish the animals for vaccination purposes. After they had been vaccinated and the vaccine pulp removed, the cattle, as was the custom, were returned to Shaw Brothers, who received a rental price for each animal and subsequently disposed of them to the public. In this particular instance the animals were vaccinated on September 23 and October 6, and turned back to Shaw Brothers October 16, on which date they were driven to the Haley Commission Company's pens in the Detroit stock yards, watered and fed for two hours, and then taken to a town 15 miles distant, where they were dispersed. The appearance of foot-and-mouth disease was observed on October 18 by Mr. I. W. Shaw, who purchased 10 of these animals, and by other purchasers about the same time.

In obtaining a record of all shipments that subsequently passed through the pens of the Haley Commission Company, which presumably became infected by the 21 vaccinated cattle, it was quite interesting to learn that the healthy cattle, previously referred to as having been collected by Mr. J. Jackson, were shipped to the Haley Commission Company on October 20 and all but 32 sold. The latter animals were reshipped to East Buffalo on October 23 and evidently carried the contagion from the infected pens of the Haley Commission Company to the Buffalo yards, and thence by means of the 7 bulls in the consignment to Watson town and Danville, Pa., as already mentioned. All subsequent centers of infection have been directly or indirectly traced to the 21 vaccinated animals as the original source of infection. All other shipments which passed through the Haley Commission Company's pens for six days previous to the receipt of the vaccinated cattle have been traced to their destinations with negative results, while negative results have also followed the investiga-

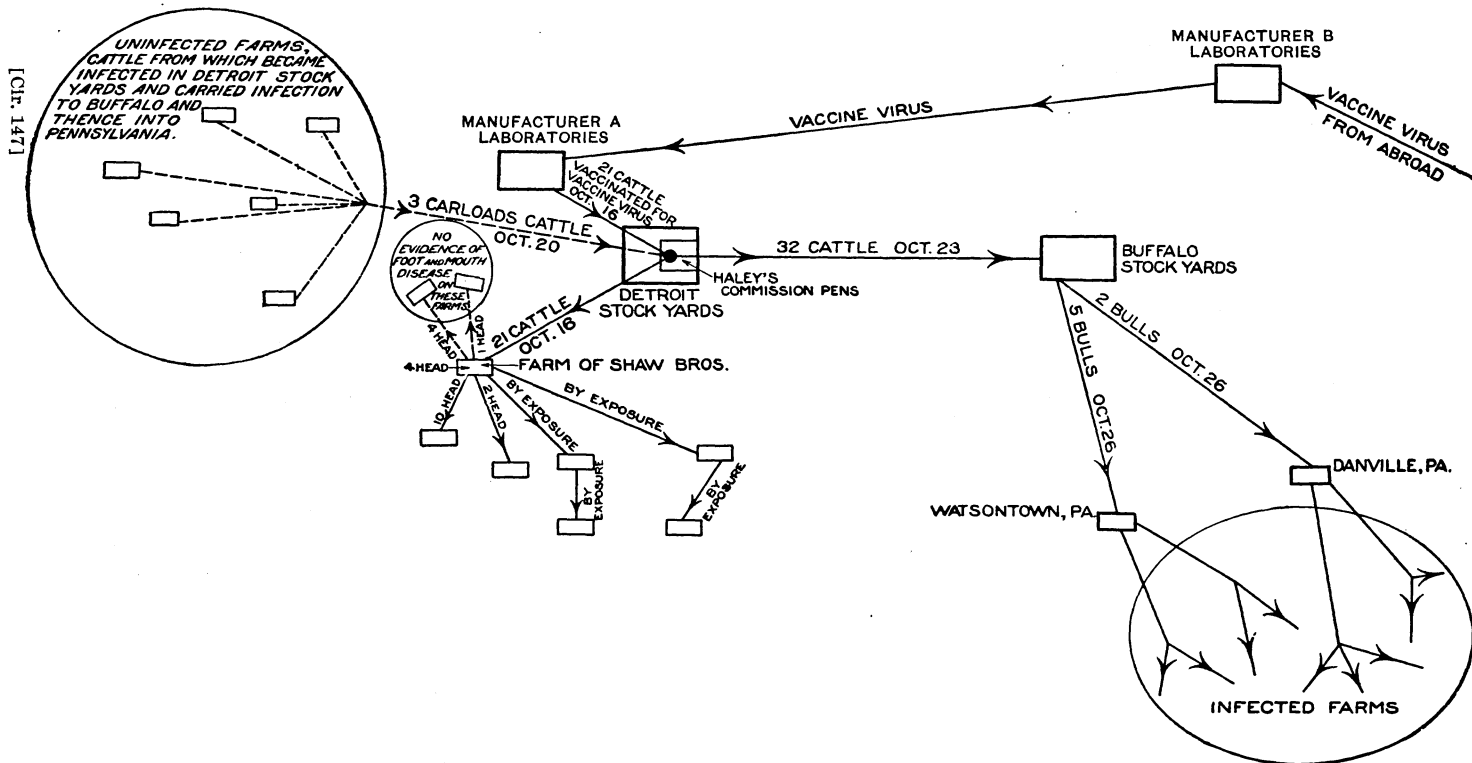


FIG. 1.—Diagram showing how infection of foot-and-mouth disease was spread. Manufacturer B imported certain vaccine virus which was contaminated with foot-and-mouth disease, and Manufacturer A procured some of B's vaccine of this strain. Calves used by A in propagating vaccine, some of which were afterwards found to be affected with foot-and-mouth disease, were sent to the Detroit stock yards and thence to certain farms near Detroit. Four days later three carloads of cattle from central Michigan reached the Detroit stock yards and were put into the pens previously occupied by the vaccine calves. Some were sold for slaughter at Detroit and the remainder were shipped to Buffalo. Nine were reshipped to Danville and Watontown, Pa., where the disease was first observed. The disease spread to various places in Pennsylvania and New York and to one locality in Maryland.

tion of places whence these 21 cattle came before they were taken to the vaccine stables of Manufacturer A.

The likelihood of the infection of these cattle through vaccination at the latter's plant having been indicated, three separate strains of vaccine virus which had been used by the firm during 1908 were secured. The experiments performed with these three lots of vaccine virus are here briefly recorded.

EXPERIMENTS WITH VACCINE VIRUS.

FIRST SERIES OF EXPERIMENTS.

These experiments with seed vaccines obtained from Manufacturer A were made jointly by the writers of this paper, assisted by Dr. E. C. Schroeder and Mr. W. E. Cotton, of the Bureau of Animal Industry, at the Bureau's Experiment Station, Bethesda, Md. A cement stable was erected for the purpose of making these tests, and special care was at all times maintained to prevent any experimental error. One attendant, who had never seen foot-and-mouth disease, and had not recently been employed among cattle or other live stock, was transferred to the work of caring for these experiment animals. All animals were kept under observation continuously for at least two weeks before the experiments were made, and in all cases the mouths and feet were carefully examined before injections were made. The three strains of vaccine virus tested in this series of experiments were obtained from Manufacturer A by the writers during a joint visit and were kept in possession of one of them (Rosenau) until the package was broken and the vials opened immediately before use. The entire work was carried out in a careful manner and every effort made to prevent outside contamination.

The clinical notes are as follows:

Calf 625.—This heifer calf, about 3 months old, was inoculated December 14, 1908, by scarifying the skin of the abdomen in three different areas, one area being inoculated with each of the strains of virus obtained from Manufacturer A and known respectively as the J strain, the D strain, and the Manufacturer B strain. This calf, which had not been previously used for producing vaccine virus, developed typical vesicles and pustules of cowpox, but did not show any indications of foot-and-mouth disease.

Three other heifer calves, Nos. 675, 676, and 674, about 5 weeks old, were inoculated intravenously December 14, 1908, with the J strain, the D strain, and the Manufacturer B strain, respectively. These animals were obtained from a local vaccine manufacturer, and having been used for the propagation of vaccine virus were immune to cowpox. Calves 675 and 676, inoculated with the J and D virus, remained healthy and failed to show any indication of disease following their injection. On the other hand, calf 674, which had been inoculated similarly with the Manufacturer B strain, developed lesions of foot-and-mouth disease as recorded in the following:

Calf 674.—December 14: Injected intravenously in right jugular vein with 2 c. c. of Manufacturer B's vaccine.

December 26: No indication of foot-and-mouth disease.

December 28: A small papule with a gray center about 2 mm. in diameter is noted on the gum of the upper jaw just above dental pad. This is the third papule of this character to make its appearance, the first being on the outside of the lower lip just at its margin, and the second inside the lower lip. All four feet from ankle down somewhat swollen and reddened.

December 29: Papule noted above has broken and left only a small eroded area. A fresh one is forming on gum of lower jaw. Swelling of feet has subsided, except in the left hind one, which is also much reduced.

3.30 p. m.: The papule noted above now has a small gray center.

December 30: The papule found yesterday appears to-day as a small erosion. Interdigital space of left hind foot reddened, other feet normal.

January 2, 1909: Two small vesicles have developed and broken on right side of tongue; one new one forming on right side of inner lower lip. Vesicles have formed and broken in interdigital space of both hind feet.

January 4: One small erosion, covered by an ulcerating surface on outside of lower lip near its margin. Lesions on side of tongue noted January 2 have disappeared. Lesions in interdigital spaces are commencing to heal.

January 7: One new hyperemic patch about 3 mm. in diameter is forming on inside of lower lip.

January 8: Lesion noted yesterday is now fairly well developed and has a gray necrotic center. One reddened papule in interdental space on right side of lower jaw.

January 18: A number of small superficial erosions, more or less circular in outline, on under side of tongue. At the peripheries of each there is a narrow zone of very thin brown epithellum, which is loosened from the basement membrane.

January 19: Erosions present on under side of tongue yesterday have partially coalesced. There are three similar circular areas on dorsum of tongue, from which the superficial layer of the mucous membrane has been eroded, leaving the papillæ still intact.

The temperature, taken twice daily since date of inoculation, has never exceeded 39.7° C.

January 20: The desquamated areas on the tongue have coalesced and increased in size. Killed. Head and left hind foot preserved as specimens.

The interesting feature in this case was the subsidence of the primary lesions and the subsequent recurrence of active erosions.

Calf 656.—December 29, 1908: Injected intravenously in right jugular vein with saliva and material from papule which had formed on gum of calf 674, mixed with sterile salt solution.

December 30, 9 a. m.: Nothing abnormal. 3.30 p. m.: A number of red papules have formed on the hard palate.

December 31: A few more slightly raised reddened areas with gray centers have developed on upper lip.

January 2, 1909: The lesions have not progressed to any further stage of development and are gradually fading away.

January 4: No lesions. The highest temperature recorded was 39.4° C.

January 9: Killed and buried immediately without autopsy.

Calf 654.—An area scarified on inside of lower lip and one on gum corresponding to it were inoculated December 29, 1908, with material scraped from papule which had formed on gum of calf 674. On the fourth day a considerable number of reddened papules formed on inside of lower and upper lips and on hard palate. Similar hyperemic zones were noted on the gums of the lower

jaw on the sixth day. These showed a dry grayish center on the following day, which on being removed left a small eroded surface without any fluid being visible. Other lesions of a similar character appeared at irregular intervals on the mucous membrane of the gums, lips, and hard palate until January 11, after which all the remaining lesions gradually disappeared. The highest temperature observed was 39.6° C. On January 20 the calf was killed and the head preserved.

Calf 623.—Inner side of lower lip scarified and inoculated January 2, 1909, with scrapings from lesions on lip of calf 654. On the fourth day several small circular areas, each covered by a gray scab, had formed at seat of scarification. These scabs disappeared on the following day, leaving small eroded areas. On the sixth day a large eroded area appeared on the dental pad and hard palate which soon became eroded and covered by a thin brownish exudate. This area increased in size on the following day coincidentally with the appearance of reddened papules on the gums, interdental space, and inside of lower lip. Similar lesions continued to appear at irregular intervals until January 23, when one or more large reddened patches were noted on nearly every transverse ridge of the hard palate. On January 25 the epithelium over these areas began to erode, the color gradually fading. Several small desquamated areas and two shallow erosions appeared on the gums behind the incisors and in the interdental space respectively. The highest temperature observed was 39.3° C. Animal killed February 27.

Cow 333.—The right side of inner surface of lower lip scarified and inoculated January 9 with material scraped from lesion in mouth of calf 623. On the second day a few small erosions partially covered with scabs appeared within area of scarification. By the fourth day several new red circular lesions of the usual character had formed within and contiguous to area of scarification. On the following day about 15 small circular erosions with gray necrotic centers were noted within and contiguous to the area of scarification. Five days later several small reddened patches appeared on the inside of the lower lip and the gums below the incisors.

January 20, injected into left jugular a small quantity of material from mouths of calves 674 and 654, which was mixed with 4 c. c. sterile salt solution. Several small reddened areas on hard palate appeared January 23. Two days later one shallow circular erosion about 8 mm. in diameter developed on gum of lower jaw. On the following day three small reddened patches with eroded centers were noted on hard palate; the small erosion still present on gum of upper jaw. About the same condition was observed three days later except that the lesions last noted were gradually disappearing. Highest temperature recorded was 39.1° C. Animal killed and buried February 11.

Calf 677.—February 5: Inside of lower lip scarified and inoculated with scrapings from the lesions of calf 623 and cow 333.

February 9: A considerable number of small, very superficial erosions within the scarified area; one a short distance outside, and another on opposite side of lower lip.

February 10: On the upper surface of tongue there are three circular areas about 3 cm. in diameter where the epithelium has become desquamated. On under side of tongue there are also two small eroded areas.

February 11: A considerable number of small red papules with small gray centers within and surrounding the seat of scarification, some of them being a considerable distance removed. On dorsum of tongue there are a number of circular and elliptical areas where the epithelium has become eroded, leaving

the papillæ and basement membrane intact. On inferior and lateral surfaces there are a number of similar raw surfaces, in some of which a narrow rim of desquamated epithelium remains attached to the periphery. The saliva is unusually thick and viscid. One small irregular erosion about the size of a bean is noted in the cleft of the left hind foot.

February 12: Many of the lesions on dorsum of tongue have coalesced; fully two-thirds of the epithelium has been desquamated. The lesions on sides and under surface of tongue have increased in size. There are a considerable number of red papules on gums of upper jaw, in the interdental space of lower jaw, and on the hard palate. The lesion in the interdigital space of the left hind foot shows no change.

February 13: Nearly all the epithelium has been stripped from the tongue. Many papules still present on inside of lip and on gums and a few new ones on hard palate. One small eroded lesion in interdigital space of each hind foot.

February 15: The epithelium of the tongue which has been exfoliated is now replaced by new tissue, leaving the tongue again normal with the exception of a small erosion on the inferior surface. There are several papules on hard palate and on inner side of lower lip. The lesions in interdigital spaces of hind feet have about disappeared.

February 16: Many red patches with eroded centers on hard palate. A few on both upper and lower lips. The highest temperature that has been recorded was 39.6° C.

March 6: No lesions apparent. On this date cow 375, occupying a corner stall in the same stable with this calf (677), was inoculated intravenously with material from the mouth of calf 609, which had been injected with vaccine from Manufacturer B.

March 11: Calf 677 has an erosion about 15 by 30 mm. on dorsum and right side of tongue and a similar one about 5 mm. in diameter a short distance in front of the other. Morning temperature, 40.3° C.; afternoon, 40° C.

March 12: The smaller area noted yesterday has increased to about 15 mm. in diameter. The longer one is about the same size as it was yesterday. Both are coated with a brownish-yellow exudate. Three additional erosions have appeared on dorsum and left side of tongue, each from 10 to 15 mm. in diameter. Three erosions, each about 12 mm. in diameter, have made their appearance on anterior portion of dental pad and upper lip near median line, and have coalesced, fragments of the desquamated epithelium being still present. Near by, on the upper lip, a vesicle about 1 cm. in diameter broke while the animal was being examined. The vesicle was very flat and appeared to be simply a circular white area in which the epithelium had become separated from the basement membrane. The amount of serum present, if any, was so small as to escape observation. On the inside of the lower lip there is a very shallow erosion about 3 mm. in diameter. No lesions on feet.

March 13: The lesions on the tongue have commenced to heal. A new eroded area has made its appearance on the buccal membrane, just back of the first molar tooth, left side. Killed at 4 p. m. A small whitish area, apparently a vesicle just forming, was found after death in the interdigital space of one of the fore feet. The head and foot was preserved in Kaiserling's fluid.

This case is particularly interesting on account of the recurrence of the lesions as a result either of autoinfection or of exposure to cow 375, which suffered from a more severe form of the disease.

Cow 375.—February 11: Moved into infected stable where the previously mentioned cases were kept to receive natural exposure to foot-and-mouth disease.

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February 11 to March 5: No lesions.

March 6, 4 p. m.: Injected intravenously with 5 c. c. of an emulsion of desquamated mucous membrane from calf 609 (see third series of experiments), which contracted foot-and-mouth disease as a result of the inoculation of Manufacturer B's vaccine.

March 10: Yesterday afternoon animal refused to eat; the flow of saliva was increased. This morning she has an erosion fully 2 cm. in diameter on side of lower lip; there is a second one about 1½ cm. in diameter on buccal membrane, immediately back of the right commissure of lips. There are also several small erosions in this region and a few on opposite side of mouth. The tongue is very sensitive and a vesicle is forming at its tip. Considerable drooling from the mouth; also clear discharge from nostrils. No lesions on feet. Animal eats very little. The temperature yesterday morning was 38.4° C.; afternoon, 39.6° C., while this morning it was 38.7° C., and remained about this height until the animal was killed (March 13). Yesterday afternoon's temperature was the highest observed during the experiment.

March 11: Large amount of ropy saliva drooling from the mouth. The two large erosions noted yesterday, which were then very red, raw-looking surfaces, are now coated with a thin grayish lymph. The several small erosions noted then have increased in size and are coated with the same kind of an exudate. Several large, white, circular vesicles have made their appearance on the dental pad. The epithellum of the entire tip of the tongue has disappeared, leaving a large raw surface. The right front foot has large vesicles filled with serum at both the front and rear of interdigital space and on bulbs of heel. The right hind foot is in a similar condition, with the exception that the vesicles have broken and serum can be pressed out of them. The left hind foot is in much the same condition as the right hind one. The left fore foot is also similarly affected, but not to the same degree as the others.

March 12: Lesions in the mouth much the same as yesterday, excepting that the white circular vesicles on the pad are now raw surfaces, the loosened epithellum having disappeared. Two additional large erosions which have coalesced found on dorsum of tongue. The vesicles on feet have nearly all broken, leaving raw and eroded surfaces partly covered by the desquamated epidermis. The animal is very lame. There is still considerable drooling from mouth.

March 13: The earlier lesions in mouth and on tip of tongue are beginning to heal. The feet are very sore, large raw surfaces being present within and behind and in front of the interdigital spaces. In some places the desquamated epidermis is still attached. Killed at 4 p. m. The head and all four feet preserved.

Cow 630.—March 10, 4 p. m.: Moved to infected stable and placed between cow 375 and calf 677 as a cohabitation experiment.

March 15: An elevated vesicle about 15 mm. in diameter has formed on left side of tongue. It has broken (10 a. m.), leaving a small opening in the center, and the desquamated epithellum is still attached at the periphery of lesion. No other lesions. The highest temperature recorded was 38.8° C., which occurred this afternoon, while the morning temperature was 38.3° C.

March 16: The epithellum is completely eroded from the area noted on tongue yesterday. The right side of upper lip is thickened, and what appears to be a spherical vesicle 2 cm. in diameter is forming and nearly ready to break on the mucous surface. On the inner surface of opposite side of the lip there is a flat vesicle about 12 mm. in diameter. On the end of tongue a slightly raised vesicle fully 2 cm. in diameter is noted. If a little pressure is exerted

in this region blood oozes from the fungiform papillæ within the affected area. There is some drooling. Animal eats fairly well. A small area within interdigital space of left front foot seems sensitive, but no lesions yet visible. Killed at 3.30 p. m. Head and left foot, the latter showing two small vesicles in interdigital space, preserved.

Calf 614.—March 13: Moved to infected stable for a natural exposure experiment after cow 375 and calf 677 had been killed. It was placed as far away from where these animals had stood as the inclosure would permit.

March 15: One erosion about 1 cm. in diameter and two raised white vesicles, each about 5 mm. in diameter, on dorsum of tongue. Two small, very fresh erosions on gums of lower jaw below the incisors.

March 16: The white vesicular elevations noted yesterday as being on the dorsum of the tongue are now erosions 15 mm. or more in diameter; the one to the right of the median line has become confluent with an erosion noted yesterday, leaving a raw surface, $1\frac{1}{2}$ by 3 cm. in diameter. Still another erosion, 1 cm. in diameter, has appeared on the dorsum of the tongue. There are now three erosions, each about 15 mm. in diameter, on gums of lower jaw below the incisors, and another 10 by 15 mm. inside of the lower lip, 2 cm. from median line. A very sensitive spot is noted within the interdigital space of the left fore foot. At 3.30 p. m.: A large amount of clear viscid fluid is being discharged from nose and mouth. It is so viscid that it hangs down in long strings from each side of the mouth. Killed. Head and left fore foot preserved. A vesicle was beginning to form on the inner side of one of the bulbs of the heel of left fore foot. The highest temperature recorded for this animal was 39.5° C., which occurred this morning.

It should be noted that in the last two instances, cow 630 and calf 614, foot-and-mouth disease obtained from vaccine virus was transmitted by natural modes of infection.

During the course of this series of experiments ample opportunity had been offered for the disease to spread to susceptible animals which cohabited with the inoculated cattle. This, however, did not occur until the introduction of the virus from calf 609 (third series of experiments) into cow 375 on March 6, where it assumed such an exalted virulence that cow 630 and calf 614 readily contracted the disease by natural exposure. For instance, calf 675 was kept in the foot-and-mouth-disease stable from December 14 until it was slaughtered on January 20; calves 676 and 625 were likewise kept in this stable from December 14 until January 9; cow 173 from January 20 to February 27; cow 375 from February 11 to March 5; hog 2449 from February 11 to February 27; sheep 34 from February 11 to February 27, and two male lambs from February 20 to March 11, but without presenting any lesions of foot-and-mouth disease. The only explanation that appears tenable for this absence of natural transmission of the disease is that the virus had become greatly attenuated, probably as a result of its admixture with vaccine virus, and it required passage through a particularly susceptible individual before it became exalted in virulence.

This same lack of virulence was observed in the disease as it occurred at the beginning of the recent outbreak. Five of the twenty-

one vaccinated calves of Manufacturer A were taken to two farms, and although they were permitted to commingle with the cattle on these farms continuously, no occurrence of the disease at these places took place. On the other hand, foot-and-mouth disease developed on every farm where the remaining sixteen cattle were taken.

In order that vaccinia (cowpox) could definitely be eliminated in making a diagnosis of the disease being produced by vaccine virus, it was thought desirable in addition to using vaccinated calves (immune to cowpox) to check the work further by inoculating guinea pigs on the scrotum and rabbits on the cornea with scrapings from the lesions produced in the calves. This was done by one of us (Mohler) in the first five cases, and the work was duplicated by the other (Rosenau) in three of the cases with entirely negative results.

It will be recalled that of the three strains of vaccine obtained from Manufacturer A, the only strain which proved to be contaminated with foot-and-mouth disease virus was obtained from Manufacturer B, and the records showed that this virus was received by Manufacturer A in May, 1908. In order to ascertain if this latter vaccine was contaminated at the time of its propagation, the establishment of Manufacturer B was visited and seed vaccine from five different lots was obtained for inoculation into sheep and calves, which experiments will be described below.

SECOND SERIES OF EXPERIMENTS.

The establishment of Manufacturer B was visited by the writers on February 1 and 2, and the records of the various vaccine seeds were examined, especially as to their origin and the character of lesions produced in the vaccinated calves. Five different lots of vaccine were obtained and experiments were at once started with a particular virus, for convenience termed "vaccine V." This strain was the same as that which had been procured by Manufacturer A. About 10 c. c. of this vaccine virus was obtained in a glass pipette, both ends of which were sealed in a flame, and the material was kept in the possession of one of us (Mohler) until used.

Sheep were used for this experiment, and they were kept in one of the animal rooms in the new laboratory building of the Department of Agriculture, where no experiments in foot-and-mouth disease had been conducted. These animals, with one exception, had been raised at the Bureau Experiment Station, and all had been under close observation for at least three weeks before the inoculations were made. This series of experiments was conducted personally by Doctor Mohler assisted by Doctor Eichhorn and an attendant who had not seen foot-and-mouth disease and had not been in any place near the infected districts. Before the pipette containing the vaccine was

opened it was submerged first in a 5 per cent solution of carbolic acid and then in 95 per cent alcohol. A small quantity of the contents was then emptied into a sterile crucible and 1 c. c. drawn up into a syringe which had just been sterilized. Every possible precaution was observed in order to prevent any outside contamination and to be able to connect definitely with the vaccine under investigation any positive results which might be obtained.

Sheep 1.—This animal was born at the Experiment Station and was about two years old. It had been vaccinated with uncontaminated vaccine virus during January and was therefore immune to vaccinia.

February 5: Injected intravenously in right jugular with 1 c. c. of Manufacturer B's vaccine V.

February 6: Temperature 39.0° C. Appetite good. No lesions.

February 7: Temperature 40.5° C. Appetite fickle. No lesions.

February 8: Temperature 40.6° C. Refuses its feed. Has been lying down since 8 a. m., when the attendant arrived. At 9 a. m. the sheep is made to rise but holds left fore foot off the ground, flexing it rapidly, apparently from pain. On walking lameness is shown in this foot and there is considerable heat noted above the coronet. On examining the interdigital space of this foot two elongated vesicles are observed, one on each claw, raising the epiderm of the soft skin, just above its attachment to the horn. On pulling the toes farther apart both vesicles ruptured, liberating a clear, watery serum. No mouth lesions.

February 9: Temperature 41.9° C. Both fore feet show erosions which extend from the anterior to the posterior border of the interdigital space, involving principally the soft skin adjacent to the coronary band. Animal is quite lame in these feet and also in the left hind foot. The latter is also found to contain an eroded elongated patch at the juncture of the skin with the horn of the hoof, and a small pea-sized vesicle is just forming in the posterior part of the cleft. No lesions in the mouth. Killed at 4 p. m. and three legs preserved. Blood defibrinated and injected into sheep 2.

Sheep 2.—February 9: This animal, a western sheep which had been under observation for 6 weeks, was injected intravenously in right jugular with 1 c. c. of filtrate of blood from sheep 1.

February 10: Temperature 39.1° C. No lesions.

February 11: Temperature 39.5° C. No lesions.

February 12: Temperature 40.1° C. The first indication of disease outside of the temperature and fickle appetite is noted to-day in that the animal is quite lame in the right front foot. On examination a small vesicle about the size of a kidney bean is observed in the front part of the cleft between the digits, while there is a hyperemic zone around the outside border of the coronet. The mouth and other feet appear normal.

February 13: Temperature 39.3° C. The vesicle which was observed in the cleft of the right front foot yesterday has ruptured and an irregular erosion with reddened base and partly covered around the borders by necrotic epiderm has taken its place. Several minute vesicles are noted above the coronary band on the outside claw, while above the heel of this claw is a moist erosion, evidently the result of a recently ruptured vesicle. No other lesions apparent, although the mouth and other feet were carefully examined. Killed at 3 p. m. Material was obtained from the vesicles and erosions for inoculation of sheep 3.

(It should be noted here that some of the filtrate obtained from sheep 1 was also injected intravenously into a cow and a Bardados sheep, but without producing any lesions. The injections of these latter cases, however, were not

made until February 11, forty-eight hours after the filtrate had been obtained, during which interval it was kept in a refrigerator.)

Sheep 3.—This animal was a yearling born at the Experiment Station and kept under close observation since January 1. Like sheep 1, it had been made immune to vaccinia by cutaneous scarification and inoculation of normal vaccine virus.

February 13: Injected intravenously in right jugular vein with 1 c. c. of fluid prepared by adding physiological salt solution to the material obtained from lesions in sheep 2.

February 14: Temperature 39.1° C. Apparently normal.

February 15: Temperature 41° C. Animal lying down most of the day. Appetite capricious. Quite sensitive if pressure is applied to cleft of left front and right hind foot.

February 16: Temperature 40.9° C. Sheep is very lame in front and particularly so in right hind leg, which is scarcely placed on the ground in walking. On examination this foot is seen to have a vesicle the size of a marrow-fat bean in the fold of skin in front of and between the digits above the interdigital space. Two erosions which are still moist and partly covered by denuded epiderm appear in the posterior part of the cleft and involving both heels. Blood is slowing oozing from the eroded surface. The left fore foot has an erosion on each claw running along the soft skin immediately above the horn of the hoof, very similar to the lesion described in the same foot of sheep 1. The right front foot shows a hyperemic area which is quite sensitive directly in the middle of the interdigital space. A small flat vesicle about the size of a split pea is forming on the glome of the inside digit. Directly in front of this on the outside coronet is a small eroded patch irregular in outline, which is covered with a grayish exudate of lymph. A marked erythema is noted above the coronary band of both digits of this foot. No mouth lesion. Animal killed at 4 p. m. Two legs preserved.

During this series of experiments sheep 4 and lamb 5 were continuously exposed to the infected sheep 1, 2, and 3, eating of the same hay, and frequently from the same feed box, but in neither case was the disease transmitted by such cohabitation. It should also be stated in passing that material from the vesicles and erosion in each of the infected sheep was rubbed well into scarified areas on the scrotum of a guinea pig and applied to the slightly abraded cornea of a rabbit, but in no case were lesions of vaccinia produced.

THIRD SERIES OF EXPERIMENTS.

This series of tests was made independently by one of us (Rosenau) in the Hygienic Laboratory, United States Public Health and Marine-Hospital Service.

The rooms in which the experiments were carried on were just finished in a new wing of the building, and had never been used for any other purpose. The inoculations were made personally by Doctor Rosenau, assisted by Doctor Frost. The care of the animals was intrusted to two janitors. None of the persons mentioned had been near any case of foot-and-mouth disease, nor had any of them had any association with cattle or sheep.

The animals used in this series were four young calves which had previously been used by a local manufacturer for the propagation of vaccine virus. They were obtained from a district entirely free from foot-and-mouth infection. They were under continuous observation for twenty days before the experiments were attempted.

The two strains of vaccine virus used in this series of experiments were personally obtained by one of us (Rosenau), who made independent trips to the establishments of Manufacturers A and B partly for this purpose, in order that there might be no connection or contamination with the virus used in the other experiments. Each strain of virus was obtained in a carefully sealed package and not opened until the moment of use. Before opening the vials they were immersed in bichlorid of mercury solution (1 to 500) in order to eliminate any outside contamination. In short, every possible precaution was taken to guard against all sources of experimental error.

Four calves, immune to vaccinia, were given an intravenous injection of the virus. The protocols are as follows:

Calf 609.—Black female, about 4 weeks old. Vaccinated, February 13. All incisions showed typical vesicles. Vaccine material taken February 19.

March 1 injected intravenously with 2 c. c. of glycerinated vaccine virus V of Manufacturer B.

On the fourth day vesicles appeared on dorsum of tongue, followed by desquamation of epithelium, leaving a large, sharply defined, and typical punched-out ulcer with deep reddened base, papillæ intact, and containing a small island of intact mucous membrane. In addition there were a few other smaller vesicles containing clear fluid. Salivation; no foot lesions; temperature rose to 39° C.; marked weakness. Animal killed on fifth day. Tongue preserved.

Calf 611.—Red male, about 5 or 6 weeks old. Vaccinated February 13. Typical take along all incisions. Vaccine material taken February 19.

March 1 given intravenous injection of 2 c. c. glycerinated vaccine virus V of Manufacturer B.

Forty-eight hours later three dark red congested macules appeared on ventral surface of tongue, two of which disappeared about twenty-four hours later; the third formed a vesicle, which ruptured within two days, leaving a superficial erosion which rapidly healed. During this time there were excessive secretion of viscid saliva and slight reddening of the margin of gums. Temperature rose to 39.6° C. on second day.

On the eighth day a small vesicle appeared on inside of upper lip, and inside of left cheek a papilla denuded of mucous membrane was noted, also three small red spots on the hard palate which continued till the animal was killed.

On the tenth day another erosion appeared on upper lip and tip of tongue.

Coincident with first appearance of these mouth lesions a small erosion appeared in the interdigital space of left hind foot, evidently a ruptured vesicle. By the eighth day the skin of the whole interdigital space of this foot was white, soft, necrotic, and perforated in several places with irregular small ulcers with reddened bases. In a corresponding position on the right hind foot appeared on the fourth day also several reddened spots and erosions.

On the ninth day a large vesicle appeared, occupying practically the whole of the interdigital space of the left fore foot, which ruptured and exuded a clear sanious fluid.

Killed on the tenth day. Specimens preserved.

Calf 610.—Red-and-white female, about four weeks old. Vaccinated February 13. All incisions showed typical vesicles. Vaccine material scraped February 19.

March 1, inoculated intravenously with 4 c. c. glycerinated vaccine virus which Manufacturer A obtained from Manufacturer B.

On the second day two small papules developed on margin of tongue, which disappeared on the fourth day. Margin of gums reddened and a small superficial erosion developed on gums near central incisor teeth. On hard palate posteriorly appeared three large reddened maculae. Centers of each spot became grayish and necrotic. Other similar patches subsequently developed on the pharynx.

An eczematous condition developed around anterior margin of interdigital clefts of both hind feet on second day, with subsequent formation of minute vesicles which quickly dried. In interdigital space of left hind foot a small vesicle appeared on the sixth day, which broke, forming an erosion which rapidly healed.

Killed on the tenth day.

Calf 612.—Red-and-white female, about five or six weeks old. Vaccinated February 13. Gave good take, all incisions showing typical vesicles, which were removed February 19.

March 1, injected intravenously with 4 c. c. glycerinated vaccine virus which Manufacturer A procured from Manufacturer B.

About the seventh day, redness of margins of gums, salivation. Small ulcer on dental pad. Small superficial ulcers on gum anteriorly and one in angle of mouth. Mucous membrane of pharynx red and congested. Mild eczematous condition of skin about interdigital cleft; no vesicles. Killed on the tenth day.

Diagnosis.—Calves 609 and 611 had typical clinical pictures of foot-and-mouth disease. The diagnosis was confirmed by Doctors Melvin, Mohler, Bennett, Eichhorn, Formad, Ditewig, and several others, who saw the animals after the lesions were well advanced.

It is believed that calves 610 and 612 also had foot-and-mouth disease of a benign type.

RESULTS SHOW CONTAMINATION OF VACCINE VIRUS.

It must appear evident from the clinical notes presented in the above three series of experiments that the vaccine virus propagated by Manufacturer B in April and May, 1908, was contaminated with the virus of foot-and-mouth disease. The history of this particular vaccine shows that it was a Japanese strain, imported for the purpose of improving the standard of vaccine produced by that company. The fact that the foot-and-mouth infection was present in the vaccine virus of Manufacturer B for so long a period, but was not transmitted to outside cattle, was doubtless due in part to this firm's practice of killing its calves after taking the vaccine virus. Manufacturer A, on the other hand, rented his calves and placed them again on the market a short time after the vaccine material was taken. In this way the disease spread from the vaccine stables of Manufacturer A, but not from those of Manufacturer B, although it was the vaccine virus from the latter establishment that infected the former's cattle.

DIFFERENTIAL DIAGNOSIS.

The clinical picture presented by the first few animals of the first series of experiments and two of the animals in the third series of experiments was somewhat confusing at first, as the disease appeared in such a benign form and the lesions were far from being typical, and further appeared at rather irregular intervals over a number of successive days rather than within a relatively short and definite period of time. We have no explanation to make of this except the fact that we were at first working with a decidedly attenuated virus of the disease. While a mistake might be made in these early cases because of the slow infection of the animal, the failure to transmit the disease by cohabitation, the presence of suggestive though atypical lesions, the absence of the characteristic vesicles and foot lesions in some of the cases, and the very conspicuous absence of general symptoms, especially drooling, inappetence, high temperature, and great loss of flesh, still such lesions as were observed must in the light of our present knowledge be considered as highly suggestive of foot-and-mouth disease.

The lesions, however, which occurred in calves 609 and 611 of the third series of experiments, sheep 1, 2, and 3 of the second series, and cows 375 and 630 and calves 677 and 614 of the first series were so entirely typical and the symptoms manifested in some of these animals were so true to the natural disease that in these cases there was no question of the diagnosis, and it so happened that three or more of these cases were observed and the diagnosis confirmed by Doctors Melvin, McEachran, Law, Pearson, White, Schroeder, Bennett, Hickman, Washburn, Eichhorn, Ditewig, Formad, and several others who have had experience with foot-and-mouth disease.

Vaccinia or cowpox was eliminated in the diagnosis by using in each series of experiments animals that had recovered from, and were therefore immune to, that disease. Furthermore, scrapings from the lesions were used for inoculating the scrotum of guinea pigs and the cornea of rabbits, but without producing any lesions of vaccinia.

Necrotic stomatitis may likewise be eliminated, as subcutaneous inoculations of rabbits were made in a number of instances for the isolation of the *Bacillus necrophorus*, but with negative results in each case.

Mycotic stomatitis was also discarded as a possible diagnosis, as the disease contaminating the vaccine virus even in the early cases was proven to be infectious and transmissible by inoculation, which is not possible with mycotic stomatitis. Furthermore, the sheep inoculated with this virus failed to develop any indications whatsoever of a stomatitis, but instead showed well-marked and typical lesions of the feet. This latter condition is one of the peculiar though character-

istic features of foot-and-mouth disease, for while the disease attacks the mouths and less frequently the feet of cattle, it seems to be localized almost exclusively in the feet of sheep.

RELATION OF FOOT-AND-MOUTH DISEASE TO VACCINE VIRUS.

Loeffler and Froesch^a in their researches upon foot-and-mouth disease show that the surest mode of infection is by the introduction of the contents of a vesicle into the circulation. It is also possible to infect by injecting the virus into the peritoneal cavity or into the musculature or by rubbing it into a scarification of the mucous membrane. On the other hand, if the virus is introduced into or under the skin, infection is very uncertain even in cattle, which are most susceptible to the disease. Infection in the latter instance seems to occur only if there is injury to the smaller blood vessels.

Loeffler and Froesch inoculated animals (cattle) with a mixture of vaccine virus and lymph from a foot-and-mouth vesicle. The result was that the animals vaccinated with this mixture only showed local reaction of vaccinia, and did not develop foot-and-mouth disease. The authors further showed that cowpox does not protect against foot-and-mouth disease nor does foot-and-mouth disease protect against cowpox. They further observed that when animals are inoculated with a mixture of the two viruses they only sicken with the general infection of foot-and-mouth disease provided blood is drawn in the cutaneous scarifications.

Hecker,^b in charge of the Saxony commission established for the study of this disease, failed to produce foot-and-mouth disease by rubbing the virus upon the healthy skin or by tying infected cotton pads to the clefts of the feet.

Recently Starcovič^c has conducted a number of experiments with the purpose of attenuating outbreaks of foot-and-mouth disease by the inoculation of the cattle with cowpox virus. This work was based upon the report of Ory, who communicated to the Société Central de Médecine Vétérinaire in Paris that material from a natural case of horsepox inoculated by cutaneous scarification into cattle confers upon them an immunity against foot-and-mouth disease. In repeating these experiments, however, Starcovič noted that the influence of either horsepox or cowpox upon the development of foot-and-mouth disease was but slight, for while the injected animals resisted exposure for an unusually long period (eighteen to twenty days), this alone would not make such vaccination practicable. With this end in view he prepared a mixture of 2 parts of cowpox virus, 2

^a Centralblatt für Bakteriologie, etc., 1. abt., vol. 23, 1898, pp. 371-391.

^b Zeitschrift der Landwirtschaftskammer für die Provinz Sachsen, No. 3, 1899.

^c Archiva Veterinaria, Nos. 4 and 5, Vol. V, p. 203.

parts of normal serum, and 1 part of foot-and-mouth disease lymph. By the injection of this mixture he succeeded in transmitting a very mild form of foot-and-mouth disease in 83 per cent of the cases, and even during the course of the disease the cattle were worked in the yoke.

In another series of experiments a mild or benign form of the disease was conveyed in 82 per cent of the cases. It was also observed that foot lesions developed only in 2 out of 17 cases, and these lesions were slight, while in the natural foot-and-mouth disease the foot lesions attain a proportion of from 60 to 70 or even 80 per cent.

As a result of these experiments Starcovici believes that with his mixture, which contains cowpox virus, a benign form of foot-and-mouth disease may be given, as a result of which the animals may be utilized without interruption in agricultural work.

Our experiments likewise indicate quite plainly that the foot-and-mouth infection in the glycerinated vaccine virus is dilute and attenuated. We have shown that the vaccine virus of Manufacturer B contained the infection of foot-and-mouth disease, and that this has existed at least since April 15, 1908, and probably a much longer time. However, no instance of the transmission of foot-and-mouth disease to man through vaccine virus has been recorded, and it is doubtful, in view of the evidence submitted, if it is possible to reproduce the disease in him by the cutaneous inoculation commonly used in the process of vaccination. Moreover, man is not very susceptible to the disease, and it would therefore seem that the virus thus contaminated may be characterized as undesirable rather than dangerous to man.

However, as soon as the facts became known immediate and effectual steps were taken by Surgeon-General Walter Wyman, of the United States Public Health and Marine-Hospital Service, to eradicate all this vaccine virus used in America. Under the law of July 1, 1902, the licenses of Manufacturers A and B were at once suspended, and all the suspected vaccine virus on hand was destroyed and that upon the market withdrawn, and other measures of a radical nature were taken to accomplish the desired object. In this process the intelligent and prompt cooperation of these firms is much to be commended. Further, the Hygienic Laboratory was directed by the Surgeon-General to examine at once every strain of vaccine virus upon the market to determine whether it was free from this infection. This has been done, and it may be stated that there is now upon the market no vaccine virus contaminated with the virus of foot-and-mouth disease. In fact, the contamination of Manufacturer A's vaccine was established while it was still undergoing the ripening process and before it had been placed on the market.

Hereafter manufacturers will be required to test their virus for the presence of foot-and-mouth infection, as they are now required to test it for the presence of tetanus and other pathogenic micro-organisms. Similar control tests will be made in the Hygienic Laboratory under the law to insure the purity and potency of the vaccine virus that is found in interstate traffic.

Furthermore, additional regulations have been issued, in accordance with section 4 of the act approved July 1, 1902, having for their specific object the prevention of the importation, or the sale in interstate traffic, of vaccine virus contaminated with foot-and-mouth disease or other infections communicable to man.

CONCLUSIONS.

(1) The recent outbreak of foot-and-mouth disease in this country started from some calves used to propagate vaccine virus.

(2) The vaccine virus used on these calves has been proved to contain the infection of foot-and-mouth disease.

(3) The outbreaks of foot-and-mouth disease in 1902-3 probably had a similar origin.

(4) It is probable that the foot-and-mouth infection got into the vaccine virus in some foreign country where the disease prevailed, and was introduced into the United States through the importation of this contaminated vaccine.

(5) The symbiosis between the infections of vaccinia and foot-and-mouth disease is especially interesting. Animals vaccinated with the mixed virus, as a rule, show only the lesions of one of these diseases, namely, vaccinia; nevertheless the infectious principle of foot-and-mouth disease remains in the vaccinal eruption.

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